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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/024,019	12/21/2001	Thomas P. Loughran JR.	USF-T154X	4345

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EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 03/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/024,019	LOUGHRAN ET AL.	
	Examiner	Art Unit	
	Jon M. Lockard	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-9,11-13,17-19 and 21-24* is/are pending in the application.

4a) Of the above claim(s) *6,7,9,18,19, 21 and 23* is/are withdrawn from consideration.

5)☒ Claim(s) *1,2,12,13,17 and 22* is/are allowed.

6)☒ Claim(s) *11 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The amendments of 20 December 2005 and 22 December 2005 have been entered in full. Claims 1-2, 6-7, 11-13, and 17-19 have been amended, claims 3, 4, and 14-16 have been cancelled, and claims 21-24 have been added.

2. Applicant's request for rejoinder of process claims 6, 7, 9, 18, 19, 21, and 23 in accordance with MPEP §821.04 is acknowledged. However, in view of the rejections set forth with respect to claim 11 of the elected invention, rejoinder is held in abeyance. Applicants are reminded that until *all* of the claims of an elected invention are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained (See MPEP §821.04). Newly added claim 24 will be examined as it reads upon the elected invention. Therefore, claims 1,2,6-9,11-13,17-19 and 21-24 are currently pending. Claims 6, 7, 9, 18, 19, 21, and 23 are withdrawn from further consideration. Claims 1, 2, 11-13, 17, 22, and 24 are the subject of this Office Action.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Withdrawn Objections and/or Rejections

4. The objections to the drawings as set forth at pg 3-4 of the previous Office Action (mailed 15 June 2005) are withdrawn in view of the amended drawings (filed 20 December 2005).

5. The objection to claims 1-4 and 11-17 for encompassing non-elected inventions is withdrawn in view of Applicants amendment of claims 1 and 2 and cancellation of claims 3, 4, and 14-16 (filed 20 December 2005).

6. The rejection of claims 4 and 14-16 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph (utility) as set forth at pg 4-12 of the previous Office Action (15 June 2005) are moot in view of Applicants cancellation of said claims (20 December 2005).

7. The rejection of claim 4 under 35 U.S.C. § 112, first paragraph (scope of enablement and written description) as set forth at pg 12-15 of the previous Office Action (15 June 2005) is moot in view of Applicants cancellation of said claim (20 December 2005).

8. The rejections of claims 3 and 16 under 35 U.S.C. 112, second paragraph, as set forth at pg 15 of the previous Office Action (15 June 2005) are moot in view of Applicants cancellation of said claims (20 December 2005).

9. The rejection of claims 2-4 and 14-17 under 35 U.S.C. § 102(e) as being anticipated by Lal et al. as set forth at pg 16 of the previous Office Action (15 June 2005) is withdrawn in view of Applicants amendment of claims 2 and 17 and cancellation of claims 3-4 and 14-16 (20 December 2005).

10. The rejection of claim 4 under 35 U.S.C. § 102(b) as being anticipated by the PRIME-IT™ Random Primer Labeling Kit as set forth at pg 17 of the previous Office Action (15 June 2005) is moot in view of Applicants cancellation of said claim (20 December 2005).

Maintained and/or New Objections and/or Rejections

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

11. Claim 11 remains rejected and newly added claim 24 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility, or a well established utility, for reasons set forth at pg 4-12 of the previous Office Action (15 June 2005).

12. Specifically, the claims are directed to a method of producing a recombinant sppr protein which comprises utilizing a nucleic acid comprising SEQ ID NO:4.

13. Applicants contend at page 9 of the response (filed 20 December 2005) that claim 11 has been amended to recite introduction of the nucleic acid molecule of claim 1, which in turn has been amended to recite a nucleic acid molecule comprising SEQ ID NO:4 or a nucleic acid sequence fully complementary to SEQ ID NO:4, and asserts the previous Office Action acknowledges the allowability of claims reciting SEQ ID NO:4.

14. Applicant's arguments have been fully considered but they are not persuasive for the following reasons. As stated at pg 4-12 of the previous Office Action (mailed 15 June 2005) and reiterated herein, the instant application discloses an isolated human sphingosine 1-phosphate receptor (SPPR) DNA sequence set forth as SEQ ID NO:4 that would at least have utility as a probe for the diagnosis of large granular lymphocyte leukemia (LGL). However, the instant specification does not teach any significance or functional characteristics of the SPPR polypeptide (SEQ ID NO:3). The specification also does not disclose any methods or working examples that indicate the claimed polynucleotides and encoded polypeptide of the instant invention are involved in any activity. There is no biological activity, phenotype, ligand, binding partner, or any other specific feature that is disclosed as being associated with the encoded SPPR

protein of SEQ ID NO:3. Without any information as to the specific properties of the encoded SPPR protein of SEQ ID NO:3, the mere identification of the polypeptide is not sufficient to impart any particular utility to the polypeptides encoded by the claimed nucleic acid molecules or produced by the claimed methods. Since significant further research would be required of the skilled artisan to determine how the polypeptide encoded by the claimed nucleic acid molecules are involved in any activities, the asserted utilities are not substantial. Since the asserted utility is not present in a ready to use, real-world application, the asserted utility is not substantial. The specification asserts the following as utilities for the claimed nucleic acid molecules and putative polypeptide (SEQ ID NO:3) encoded by the claimed nucleic acid molecules or produced by the claimed methods:

> 1) the SPPR polypeptide can be used to screen ligands, agonists, and antagonists of SPPR (pg 3, lines 3-4);
>
> 2) the SPPR gene can be used to produce SPPR protein, which can be used in developing therapeutic agents for various diseases (pg 3, lines 8-10);
>
> 3) the SPPR protein can be used in elucidating the mechanisms of immunosuppression in living bodies (pg 7, line 23);
>
> 4) the SPPR protein can be used in developing or screening therapeutic agents for autoimmune diseases, such as rheumatism, systemic lupus erythematodes, and LGL, for example (pg 7, lines 24-25); and
>
> 5) the SPPR protein can be used in elucidating the mechanisms of neurodegeneration in living bodies, developing or screening out therapeutic agents for neurodegenerative diseases, searching for endogenous ligands and substrates to the novel protein, and developing therapeutic agents therefore (pg 7, lines 27-31.

Each of these shall be addressed in turn.

1) to screen for ligands, agonists, and antagonists. This asserted utility is not specific or substantial. Since such assays can be performed with any polypeptide, the asserted utility is not

specific to the SPPR polypeptide encoded by the claimed nucleic acid molecules. Additionally, the specification discloses nothing specific or substantial for the proteins or other binding partners that can be identified by this method. This would constitute further research to determine the properties of the polypeptide, which clearly is of the type of experimentation that does not meet the requirements of 35 USC § 101.

2) to produce a SPPR polypeptide. This asserted utility is not specific or substantial. Since the same assays can be performed with any polypeptide, the asserted utility is not specific to the SPPR polypeptide encoded by the claimed nucleic acid molecules. Furthermore, the specification does not disclose any disorders that are associated with altered levels or forms of the SPPR polypeptide. Since the asserted utility is not presented in a ready to use, real-world application, the asserted utility is not substantial.

3) elucidating the mechanisms of immunosuppression. This asserted utility is not specific or substantial. The specification does not disclose any disorders that are associated with altered levels or forms of the SPPR polypeptide. Since the asserted utility is not presented in a ready to use, real-world application, the asserted utility is not substantial.

4) developing or screening therapeutic agents for autoimmune diseases. This asserted utility is not specific or substantial. Since such assays can be performed with any polypeptide, the asserted utility is not specific to the SPPR polypeptide encoded by the claimed nucleic acid molecules. Additionally, the specification discloses nothing specific or substantial for the agents that can be identified by this method. This would constitute further research to determine the properties of the polypeptide, which clearly is of the type of experimentation that does not meet the requirements of 35 USC § 101.

5) elucidating the mechanisms of neurodegeneration in living bodies, developing or screening out therapeutic agents for neurodegenerative diseases, searching for endogenous ligands and substrates to the novel protein, and developing therapeutic agents therefore. This asserted utility is not specific or substantial. The specification does not disclose any disorders that are associated with altered levels or forms of the SPPR polypeptide. Furthermore, since such assays can be performed with any polypeptide, the asserted utility is not specific to the SPPR polypeptide encoded by the claimed nucleic acid molecules. Additionally, the specification discloses nothing specific or substantial for the agents that can be identified by this method. This would constitute further research to determine the properties of the polypeptide, which clearly is of the type of experimentation that does not meet the requirements of 35 USC § 101.

15. The specification teaches that the results from the microarray analysis using mRNA isolated from peripheral blood mononuclear cells (PBMCs) from LGL leukemia patients and mRNA from normal individuals demonstrate that SPPR is overexpressed in LGL leukemia patients ((See pg 2, lines 11-14; pg 3, lines 15-23). The specification also teaches that the results from the microarray analysis were confirmed with Northern blot analysis using RNA isolated from PBMCs of LGL leukemia patients and normal individuals (See pg 5, lines 22-28). However, even though the data have clearly demonstrated upregulation of SPPR mRNA in LGL leukemia, such would not be indicative of a use of the SPPR polypeptide encoded by the claimed nucleic acid molecules. The preliminary data were not supported by analysis of protein expression. More importantly, the art teaches that it does not necessarily follow that an increase

in DNA or mRNA copy number results in increased polypeptide expression, such that the SPPR polypeptide would be useful as a drug target to treat autoimmune or neurodegenerative disorders. For example, as discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871; previously cited), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (Journal of Proteome Research 2: 405-412, 2003; previously cited) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (pg 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Similarly, Chen et al. (2002, Molecular and Cellular Proteomics 1: 304-313; previously cited) disclose that twenty-eight of the 165 protein blots (17%) or 21 of 98 genes (21.4%) had a statistically significant correlation between protein and mRNA expression (see Abstract and Table I). In addition, their results showed that no significant correlation between mRNA and protein expression was found ($r = -0.025$), if the average levels of mRNA or protein among all samples were applied across the 165 protein blots (98 genes). The reference also teaches that the mRNA/protein correlation coefficient varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of protein abundance. In this

study using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, it is showed that only a minority subset of the proteins exhibited a significant positive correlation with mRNA abundance. Therefore, data pertaining to SPPR nucleic acids do not necessarily indicate anything significant regarding the SPPR polypeptides. Thus, the data do not support the implicit assertion that compounds that modulate the activity of the SPPR polypeptide can be used to treat autoimmune or neurodegenerative disorders, and the art indicates that it is not the norm that gene amplification, or even increased transcription, results in increased protein levels. Since the SPPR polypeptides do not have a specific, substantial, or well-established utility, the methods of producing the SPPR polypeptide have no utility.

16. Thus, the identification that SPPR mRNA is overexpressed in LGL leukemia would not be accepted by those of skill in the art as being predictive of the function of the SPPR polypeptide. Utility must be in readily available form. It is possible that, after further characterization, this protein might be found to have a patentable utility, in which case proteins would have a specific utility, or the protein might be found to be associated with a specific disease. This further characterization, however, is part of the act of the invention, and until it has been undertaken, Applicant's claimed invention is incomplete. Because the instant specification has failed to identify a physiological process which has been shown to be influenced by the activation or inhibition of the SPPR protein of the instant invention, an artisan would have no way of predicting what effects the administration of an agent which modulates its activity would have. If one cannot predict the effects that the administration of a ligand of the SPPR protein of the instant invention is going to have on an organism, then it is unclear as to what practical or real-world benefit is derived by the public from the identification of that ligand.

17. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct., 1966), in which a novel compound that was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

18. Claim 11 remains and newly added claim 24 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to make/use the claimed invention.

19. Furthermore, even if claim 11 was found to be enabling, it would remain rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably provide enablement for the full scope of the claim. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

20. Claim 11 is drawn to a method for producing a recombinant sppr protein which comprises introducing the nucleic acid molecule of claim 1 into a host to thereby transform said host, cultivating the thus-obtained transformant, and recovering the recombinant sppr protein thus produced. However, claim 1 also recites "a nucleic acid sequence fully complementary to SEQ ID NO:4", and the specification has not taught how to make a protein using "a complement" of the cDNA (SEQ ID NO:4) encoding a protein having the amino acid sequence of SEQ ID NO:3. As the specification does not teach how to make and use a number of species that would be commensurate in scope with the claim, it is found that it would require undue experimentation to practice the invention in a manner commensurate in scope with the claim, given the lack of guidance in the specification and the very broad scope of the claim.

Claim Rejections - 35 USC § 112, 2nd Paragraph

21. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

22. Claim 11 is rejected as being indefinite for reciting "the nucleic acid of claim 1". Since claim 1 recites 2 different nucleic acid sequences, i.e., a nucleic acid molecule comprising SEQ ID NO:4 and a nucleic acid sequence that is fully complementary to SEQ ID NO:4, it is unclear what nucleic acid is being referred to in the claim.

Summary

Allowable Subject Matter

23. Claims 1, 2, 12, 13, 17, and 22 would appear to be allowable as the prior art does not teach or suggest the particular species of nucleic acid molecule, and vectors and host cells comprising the same.

24. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

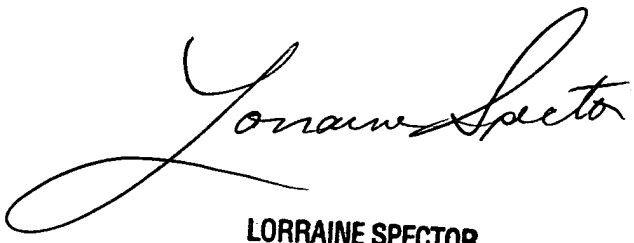
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard, Ph.D.** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback**, can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

JML
February 23, 2006



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